Cell
Leading Edge
Essay

Tetherin: Holding On and Letting Go

Daniel Sauter,[1] Anke Specht,[1] and Frank Kirchhoff[1,*]
[1]Institute of Molecular Virology, University Clinic Ulm, Meyerhofstrasse 1, 89081 Ulm, Germany
*Correspondence: frank.kirchhoff@uni-ulm.de
DOI 10.1016/j.cell.2010.04.022

Mammalian cells are equipped with so-called "restriction factors" that suppress virus replication and help to prevent virus transmission from one species to another. This Essay discusses the host restriction factor tetherin, which blocks the release of enveloped viruses like HIV-1, and the factors evolved by primate lentiviruses, such as Vpu and Nef, that antagonize tetherin's action.

Constant exposure to a wide variety of viral pathogens during human evolution has shaped our genetic material. Indeed, ~8% of our genome consists of the defective remnants of once-infectious retroviruses. Recent data suggest that these continuous encounters with viral pathogens over millions of years have driven the evolution of antiviral host factors that may help to control virus spread and to prevent cross-species transmission of viral pathogens. These so called "host restriction" factors are components of the innate immune response and interfere with different stages of the virus life cycle. They can be constitutively expressed or may be induced by interferon-α (IFN-α) during induction of the innate immune response by viral infection. There are three main classes of restriction factors that are effective against retroviruses: cytidine deaminases such as APOBEC3G (apolipoprotein B mRNA-editing enzyme 3G), which induces lethal hypermutations in the retroviral genome; TRIM5α (tripartite motif protein 5α) proteins, which restrict the incoming retroviral capsid; and tetherin (also known as BST-2, CD317, or HM1.24), which impedes the release of newly formed virions of human immunodeficiency virus (HIV-1) and other enveloped viruses from the host cell surface (Malim and Emerman, 2008; Neil and Bieniasz, 2009). Usually, these factors efficiently restrict retroviral infection, but, as a counterstrike, viruses have evolved specific antagonists to oppose their action. For example, in HIV-1 and the closely related simian immunodeficiency viruses (SIVs), the viral proteins Vpu or Nef interfere with the action of tetherin. Here, we summarize our current knowledge of tetherin and speculate on its possible role in the pathogenesis and spread of HIV-1.

Tetherin: Structure and Function

The host restriction factor tetherin was discovered a few years ago by the groups of Bieniasz and Guatelli (Neil et al., 2008; Van Damme et al., 2008). It has long been known that the Vpu protein of HIV-1 is required for efficient release of viral particles from certain cell types (e.g., HeLa cells) but not from others (e.g., COS-7 cells) (Strebel et al., 1989; Göttlinger et al., 1993). Heterokaryons formed between HeLa cells and COS-7 cells showed the characteristics of HeLa cells, suggesting the expression of a dominant restrictive factor that is antagonized by Vpu (Varthakavi et al., 2003). This factor is induced by type I interferons and efficiently tethers virions to the host cell surface (Neil et al., 2007). Bieniasz and colleagues identified this factor as BST-2/tetherin by using microarray analyses to compare the expression of genes encoding membrane-associated proteins that were constitutively expressed in cells where Vpu was required for efficient virion release versus cells where Vpu was only required after IFN-α treatment (Neil et al., 2008). Independently, Van Damme et al. (2008) identified BST-2/tetherin by extending work showing that BST-2 is downmodulated by the Vpu protein of HIV-1 and by the K5 protein of Kaposi's sarcoma associated herpes virus (KSHV) (Bartee et al., 2006).

Tetherin is a 30–36 kDa type II single-pass transmembrane protein. It comprises a cytoplasmic N-terminal region, followed by a transmembrane domain, a coiled-coil extracellular domain, and a C-terminal glycosylphosphatidylinositol (GPI) anchor (Kupzig et al., 2003). The ectodomain of tetherin contains two N-linked glycosylation sites and three cysteine residues that mediate homodimerization. The extracellular core region of tetherin forms a parallel disulfide-linked coiled-coil domain, and the entire extracellular domain may adopt an extended 170 Å long rod-like structure (Hinz et al., 2010). Interestingly, the coiled-coil domain of tetherin contains several conserved destabilizing amino acid residues, possibly providing sufficient conformational flexibility to enable the GPI anchor to be inserted into the budding virion envelope and the transmembrane domain to be embedded in the host cell plasma membrane. The topology of tetherin with both a GPI anchor and a transmembrane domain is highly unusual and is only shared by an isoform of the prion protein (Moore et al., 1999). Notably, the GPI anchor enables tetherin to be targeted to cholesterol-rich lipid rafts in the plasma membrane (Kupzig et al., 2003), the preferential site for HIV virion budding.

Tetherin is usually only expressed efficiently in plasmacytoid dendritic cells, some cancer cells, terminally differentiated B cells, and bone marrow stromal cells (Blasius et al., 2006). However, its expression is strongly induced by type I IFNs (Neil et al., 2007). Induction of IFN expression by HIV-1 in vitro involves binding of HIV-1 virions to the CD4 receptor on plasmacytoid dendritic cells (the major producers of IFN), endocytosis of the virions, and triggering of Toll-like receptors (TLRs) 7 and 9 by viral nucleic acids in endosomes

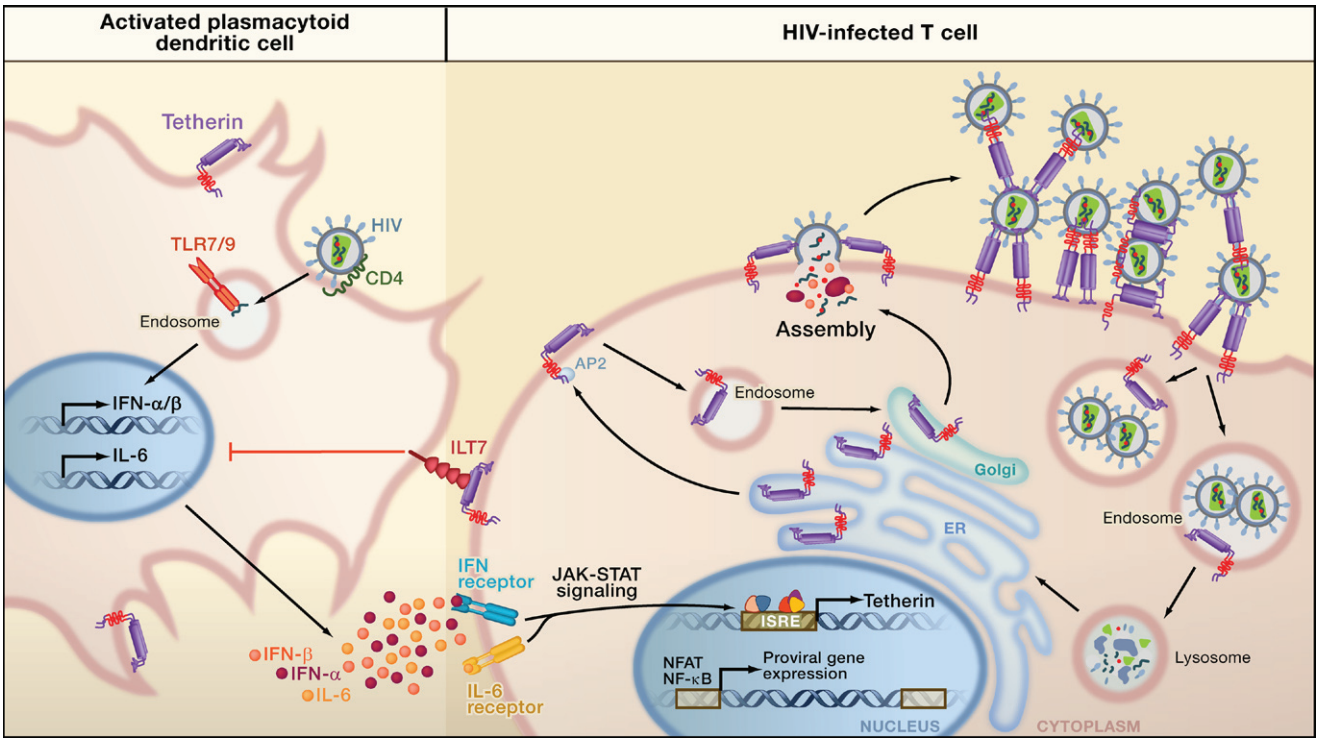

Figure 1. Tetherin and Antiviral Activity

HIV-1 infection induces production of interferons (IFNs) by plasmacytoid dendritic cells in the host. HIV-1 first binds to the CD4 receptor expressed by these dendritic cells, is endocytosed, and then the viral RNA/DNA binds and activates Toll-like receptors (TLRs) 7 and 9 in endosomes resulting in the expression of IFN genes. IFN-α and IFN-β induce expression of tetherin via the JAK/STAT signaling pathway. Tetherin cycles between the trans-Golgi network and the cell surface; it binds to ILT7 to prevent overproduction of proinflammatory cytokines by plasmacytoid dendritic cells through a negative feedback loop. Tetherin blocks release of budding HIV-1 virions by inserting one or both of its membrane anchors into the envelope of the virions, thus anchoring them to the host cell surface. This results in the endocytosis and (most likely) lysosomal degradation of the virus particles. In the case of HIV-1, the Vpu protein of the virus antagonizes the action of tetherin (not shown). ISRE, interferon-stimulated response element.

(Figure 1) (Beignon et al., 2005; Haupt et al., 2008; Mandl et al., 2008). Type I IFNs induce expression of several hundred different genes and activate natural killer cells, myeloid dendritic cells, T and B cells, and macrophages. Tetherin expression is induced by the JAK/STAT signaling pathway after binding of IFN-α and IFN-β to their receptors (Figure 1). Notably, the tetherin gene promoter contains various response elements, suggesting that other inflammatory cytokines, such as IL-6 and TNFα, may also induce its expression. Tetherin moves cotranslationally into the endoplasmic reticulum (ER) and is transported first to the compartments of the Golgi apparatus via COPII-coated vesicles and finally to the plasma membrane (Figure 1). It binds to AP2 adaptor complexes via conserved tyrosines in its cytoplasmic tail, is internalized via clathrin-mediated endocytosis, and cycles between the cell surface and the trans-Golgi network (Rollason et al., 2007). To prevent immune hyperactivation, tetherin binds to immunoglobulin-like transcript 7 (ILT7) on plasmacytoid dendritic cells and inhibits the expression of type I IFNs and other proinflammatory cytokines in a negative feedback loop (Cao et al., 2009).

Tetherin's Antiviral Action

The inefficient release of HIV-1 virions in the absence of the viral factor Vpu as a result of the action of tetherin is associated with the accumulation of virions at the plasma membrane and within intracellular clathrin-coated endosomal structures (Neil et al., 2006). The virions trapped at the cell surface are infectious and can be released by physical shearing or subtilisin treatment (Neil et al., 2006; Kaletsky et al., 2009). Importantly, the inhibitory mechanism is relatively nonspecific, as tetherin restricts the release of different retroviruses, including alpha-, beta-, delta-, spuma-, and lentiviruses, arenaviruses (Lassa), filoviruses (Marburg, Ebola), and herpesviruses (KSHV) (Göttlinger et al., 1993; Jouvenet et al., 2009; Sakuma et al., 2009; Mansouri et al., 2009; Kaletsky et al., 2009; Neil et al., 2008).

The fact that tetherin contains two membrane anchors suggests that it may directly tether newly forming virions to host cells. Bieniasz and colleagues have shown that it is the unusual structure of tetherin and not the primary sequence that determines its antiviral activity (Perez-Caballero et al., 2009). These authors generated an artificial protein with a different amino acid sequence but comparable topology and found that it efficiently inhibits virus release. Thus, tetherin may not need a cofactor but rather tethers virions directly to the plasma membrane and to one another (Figure 1). This simple mechanism is in agreement with the

finding that removal of either the cytoplasmic tail or the GPI anchor abolishes the antiviral activity of tetherin (Neil et al., 2008). It is not yet clear whether it is the transmembrane domain or the GPI anchor of tetherin that is inserted into the viral envelope. However, the observation that tetherin can also tether virions to one another implies that both domains can be incorporated into viral membranes. But many questions remain including the role of dimerization in the tethering mechanism. Dimerization seems to be critical for tetherin's inhibition of the release of HIV-1 virions (Perez-Caballero et al., 2009) but not of filovirus particles (Sakuma et al., 2009). Furthermore, it is still not clear whether the association of tetherin with lipid rafts and its interaction with the actin cytoskeleton help to recruit this restriction factor to sites of virus budding (Kupzig et al., 2003; Rollason et al., 2009). Recent data suggest that the RING-type E3 ubiquitin ligase breast cancer-associated gene 2 (BCA2; also called Rabring7, ZNF364, or RNF115) accelerates the internalization and degradation of tethered HIV-1 virions and may thus be a cofactor for tetherin (Miyakawa et al., 2009). Also, it is not known whether endocytosed tethered virions are generally degraded in lysosomes or whether they may remain intact and cycle back to the cell surface.

Vpu Antagonizes Tetherin

Tetherin was discovered because it is antagonized by the HIV-1 protein Vpu. This accessory viral factor is a 16 kDa type 1 transmembrane protein that seems to interact directly with the transmembrane domain of tetherin. This interaction is highly specific as single point mutations in tetherin's transmembrane domain render it resistant to Vpu (McNatt et al., 2009; Gupta et al., 2009). Vpu leads to moderately reduced levels of tetherin at the host cell surface and a modest decrease in total cellular tetherin (Van Damme et al., 2008; Mitchell et al., 2009; Douglas et al., 2009). This may be achieved by targeting tetherin to the trans-Golgi network or to early endosomes for proteasomal or lysosomal degradation by a β-TrCP-dependent mechanism (Douglas et al., 2009; Goffinet et al., 2009; Gupta et al., 2009; Mangeat et al., 2009) (Table S1 available online). However, mutations in the TrCP-binding motif in Vpu do not entirely disrupt its ability to antagonize tetherin and promote virion release (Schubert and Strebel, 1994; Van Damme et al., 2008), and downmodulation of tetherin may not always be required for Vpu to promote virion release (Miyagi et al., 2009; Neil et al., 2008; Dubé et al., 2010). Thus, the exact mechanisms of tetherin downmodulation from the cell surface and intracellular degradation or sequestration, as well as the relative contribution of these effects to Vpu-dependent enhancement of virion release, remain to be determined.

Most primate lentiviruses do not contain a *vpu* gene. Indeed, some primate lentiviruses (e.g., SIVsmm, SIVmac, SIVsyk, and SIVagm from sooty mangabeys, macaques, Syke's monkeys, and African green monkeys, respectively) use their Nef proteins to antagonize tetherin (Jia et al., 2009; Sauter et al., 2009; Zhang et al., 2009). Surprisingly, SIVcpz from chimpanzees and SIVgor from gorillas, which contain Vpu and are the ancestors of HIV-1, also use Nef to block tetherin. Nef is a myristoylated protein that is critical for efficient viral replication in vivo and manipulates cellular trafficking, signal transduction, and gene expression in host cells. How Nef antagonizes tetherin is unclear, but Nef is known to act as an adaptor protein, interacting with the cytoplasmic domains of CD4, CD28, and class I MHC molecules and downmodulating their expression by recruiting them to the endocytic machinery or re-routing them to lysosomes for degradation. Nef also targets the cytoplasmic tail of tetherin and reduces its expression at the host cell surface (Jia et al., 2009; Zhang et al., 2009). Certain mutations in Nef that disrupt its effect on tetherin also abolish CD4 downregulation implicating a similar mechanism in both events, such as AP2-dependent endocytosis and lysosomal degradation.

In contrast to its direct simian precursor (SIVsmm from naturally infected sooty mangabeys; Gao et al., 1992), HIV-2 uses its envelope glycoprotein Env (and not Nef) to antagonize tetherin by sequestering it away from sites of virus assembly (Le Tortorec and Neil, 2009). The Env glycoprotein of HIV-2 seems to interact directly with the ectodomain of tetherin, and its ability to promote virus release requires an intact Gyxxθ motif that binds to AP2 and targets it for clathrin-mediated endocytosis. Interestingly, SIVtan from Tantalus monkeys uses both Env and Nef to antagonize tetherin (Gupta et al., 2009; Zhang et al., 2009). It is not known whether simple retroviruses that do not encode Vpu or Nef can use Env to counteract tetherin or whether they do not require a tetherin antagonist because they do not induce an inflammatory type I IFN response. Herpesviruses and filoviruses encode tetherin antagonists; KSHV uses K5/MIR2, a viral member of the membrane-associated RING-CH ubiquitin ligase family, to ubiquitinate tetherin at lysines K18 and K28 and target it for degradation (Mansouri et al., 2009). Tetherin-mediated restriction of filovirus budding is antagonized by the Ebola virus glycoprotein (Kaletsky et al., 2009), but this does not seem to involve a reduction in tetherin expression. Like the HIV-2 and SIVtan Env glycoproteins, the Ebola virus glycoprotein may sequester tetherin away from the site of virus budding (Table S1).

Tetherin and Primate Lentivirus Evolution

Genes encoding host restriction factors show strong evidence for positive selection and have evolved rapidly. This diversifying selection is most likely driven by the need to combat new emerging pathogens or new viral antagonist proteins. As a consequence, these antiviral factors show a high degree of sequence divergence and may constitute barriers to zoonotic viral transmission from animal reservoirs because the viral antagonists often act in a species-specific manner. For example, the HIV-1 Vpu protein antagonizes human but not monkey tetherin (Gupta et al., 2009; McNatt et al., 2009), whereas the Vpu proteins of SIVgsn, SIVmon, and SIVmus show the opposite phenotype and counteract monkey but not human or ape tetherins (Sauter et al., 2009). However, primate lentiviruses are well known for their ability to cross species barriers and to adapt rapidly to a new host environment (Figure 2A). SIVcpz most likely arose from a recombination event between ancestors of SIVs that presently infect Red-capped

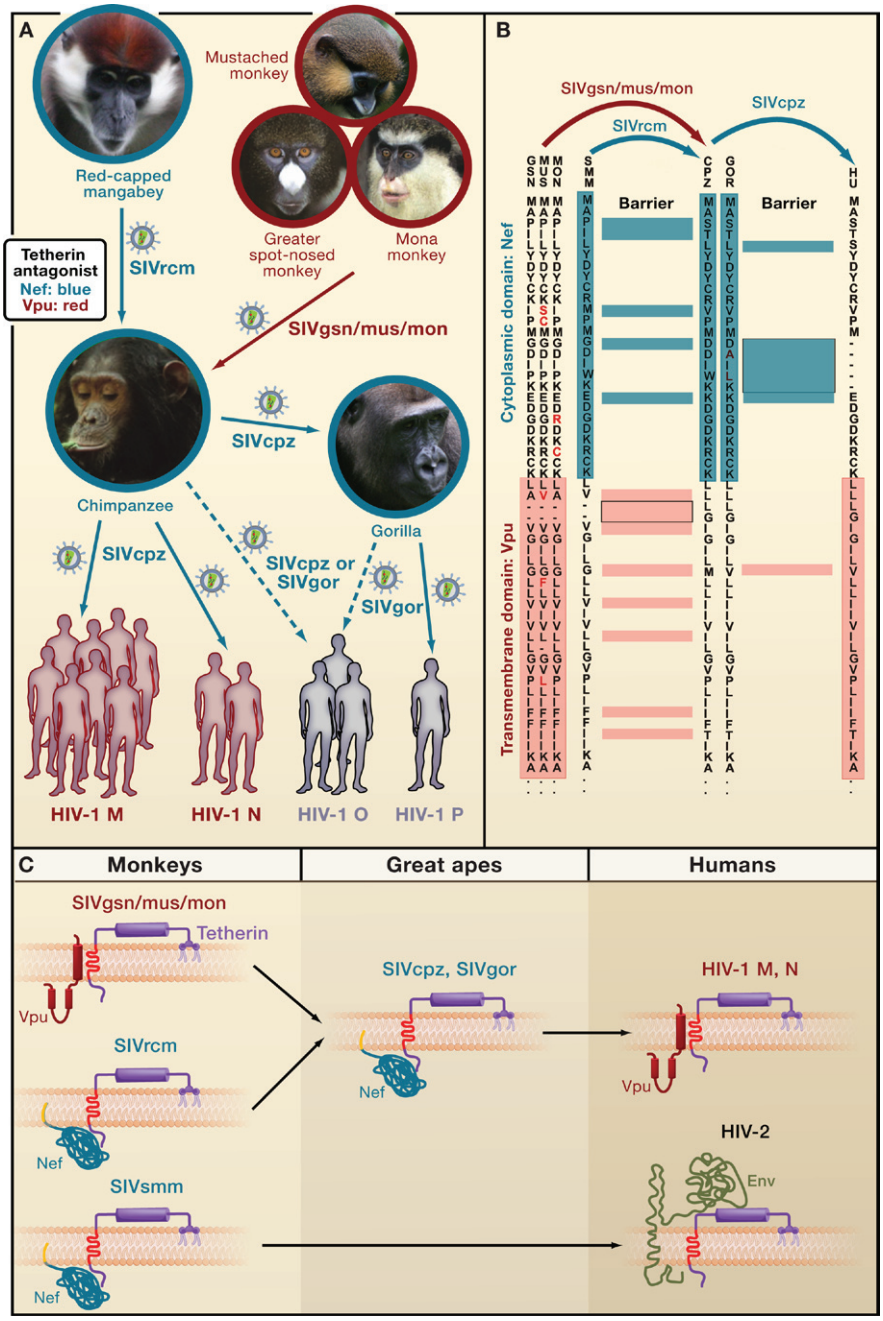

Figure 2. Tetherin and Lentivirus Evolution

Viral antagonists of tetherin in the primate lentiviral lineages from which HIV-1 arose.

(A) The simian immunodeficiency virus (SIV) of chimpanzees (SIVcpz) is thought to be a recombinant between the predecessor of SIVrcm found in Red-capped mangabeys and the common *vpu*-containing ancestor of SIVgsn, SIVmus, and SIVmon that currently infect Greater spot-nosed, Mustached, and Mona monkeys (Bailes et al., 2003). Chimpanzees prey on these monkeys explaining why they became coinfected with both simian viruses. SIVcpz was later transmitted to humans and gorillas, evolving into HIV-1 and SIVgor, respectively. It is not known whether HIV-1 group O strains originated from chimpanzees or gorillas (dashed line). The host restriction factor tetherin is antagonized by the viral protein Vpu (red) or Nef (blue) depending on the SIV or HIV strain.

(B) Alignment of the amino acid sequences of the N-terminal region of tetherin from Greater spot-nosed monkeys (GSN), Mustached monkeys (MUS), Mona monkeys (MON), sooty mangabeys (SMM), chimpanzees (CPZ), gorillas (GOR), and humans (HU). Shown are the cytoplasmic and transmembrane domains targeted by Nef and Vpu. Amino acid differences and deletions (framed) that may pose barriers to cross-species virus transmission are highlighted by boxes. (The tetherin sequence of the sooty mangabey is shown as that of the Red-capped mangabey is not available.)

(C) Switches between Vpu-, Nef-, and Env-dependent antagonism of tetherin in SIV strains that preceded the emergence of HIV-1 and HIV-2. Vpu interacts with tetherin via its transmembrane domain. Nef interacts with the cytoplasmic domain of tetherin, which contains a deletion in the human protein but not in the tetherins of nonhuman primates. The interaction site for HIV-2 Env and human tetherin is unknown but may be located in tetherin's ectodomain. Photos courtesy of M.L. Wilson, Cecile Neel, and Martine Peeters.

mangabeys and *Cercopithecus* monkeys (Bailes et al., 2003). Subsequently, SIVcpz was transmitted from chimpanzees to gorillas, giving rise to SIVgor, and to humans, giving rise to pandemic group M, rare group N, and (possibly) nonpandemic group O strains of HIV-1 (Van Heuverswyn and Peeters, 2007). A new virus (designated HIV-1 group P) that is closely related to SIVgor and most likely was transmitted from gorillas to humans has been recently identified (Plantier et al., 2009).

How do these primate lentiviruses antagonize tetherin? The ancestor of SIVrcm most likely used Nef to antagonize tetherin (because SIVrcm does not have Vpu), and the ancestor of the SIVgsn/mus/mon lineage most probably used Vpu (because its descendants do) (Sauter et al., 2009). Phylogenetic analyses suggest that SIVcpz received the *vpu* gene from the predecessor of the SIVgsn/mus/mon lineage and *nef* from the SIVrcm lineage (Schindler et al., 2006). The transmembrane domain of chimpanzee and monkey tetherin that is targeted by Vpu differs by seven amino acids and a small deletion (Figure 2B). The cytoplasmic domain of tetherin that seems to interact with Nef is less divergent, which may explain why Nef and not Vpu evolved to become an effective tetherin antagonist in SIVcpz-infected chimpanzees.

After zoonotic transmission of SIVcpz from chimpanzees to gorillas the Nef of SIVgor was able to adapt rapidly to antagonize gorilla tetherin because the cytoplasmic domain of gorilla and chimpanzee tetherin differs by only two amino acids. However, human tetherin is resistant to Nef because there is a five amino acid deletion in its cytoplasmic domain (Figure 2B), which may have evolved to escape the protein antagonists of ancient lentiviruses (Zhang et al., 2009). This deletion poses a significant barrier for viral transmission from chimpanzees to humans

and most likely forced HIV-1 to switch from Nef to Vpu to counteract tetherin in its new human host (Figure 2C). Notably, only pandemic HIV-1 M strains mastered this hurdle perfectly by regaining efficient Vpu-mediated antitetherin activity. In contrast, the Vpu proteins of HIV-1 O and P strains are poor tetherin antagonists, and those of the rare HIV-1 group N strains gained some antitetherin activity but lost the ability to degrade CD4 (Sauter et al., 2009; D.S., A.S., and F.K., unpublished data). The sequence variations underlying these differences in Vpu function among the different HIV-1 strains remain to be elucidated. The resistance of human tetherin to Nef may also explain why HIV-2, which originated from SIVsmm, switched from Nef to the Env glycoprotein in order to suppress tetherin's action (Le Tortorec and Neil, 2009) (Figure 2C).

Tetherin and HIV-1 Pathogenesis

The fact that viruses have developed highly specific tools to antagonize tetherin clearly suggests that this host restriction factor is a significant inhibitor of virus replication in vivo. However, the importance of the type I IFN immune response and of tetherin antagonists for control of HIV-1 replication in vivo and for HIV-1 pathogenesis remains to be fully defined. Chimeric SIVmac constructs expressing the HIV-1 *nef* gene (SHIV) can cause fatal disease in macaques (Alexander et al., 1999; Kirchhoff et al., 1999), although the Nef of HIV-1 is unable to antagonize tetherin. HIV-1 O strains show reduced replicative fitness in cell culture and spread less efficiently in the human population than the HIV-1 M strain but can cause AIDS (Mauclère et al., 1997) even though their Vpu and Nef proteins are poor tetherin antagonists (Sauter et al., 2009). It remains to be clarified whether the HIV-1 Nef protein acquired antitetherin activity in SHIV-infected macaques and whether HIV-1 O strains may use another protein to antagonize tetherin. Nonetheless, these findings raise the possibility that effective tetherin antagonism may not be obligatory for efficient viral replication and disease progression in vivo. One possible reason for the presumably limited relevance of tetherin to HIV-1 pathogenesis and the development of AIDS is that tetherin and other host restriction factors may inhibit the cell-to-cell spread of virus (a potent means of virus replication in vivo) less efficiently than the spread of cell-free virions (Vendrame et al., 2009). *Vpu*-defective HIV-1 shows enhanced cell-to-cell transmission (Gummuluru et al., 2000), and tetherin has been detected in biofilm-like extracellular viral assemblies that mediate cell-to-cell transmission of the lentivirus HTLV-1 (Pais-Correia et al., 2010). However, HIV-1 mutants lacking Vpu replicate less effectively than wild-type virus in ex vivo-infected human lymphoid tissues (Schindler et al., 2010). Thus, further studies on the effect of tetherin on the cell-to-cell spread of viruses are warranted. The finding that only Vpu proteins of pandemic HIV-1 M strains are effective against both tetherin and CD4 suggests a role for these Vpu functions in sexual transmission of HIV-1 within the human population, possibly by affecting the shedding of infectious virions into genital fluids. Further studies comparing the rates of virus transmission and disease progression in infections caused by HIV-1 M and O (and as far as possible N and P) strains are needed to clarify the importance of tetherin antagonism and Vpu-mediated CD4 degradation in vivo.

Tetherin and Antiretroviral Therapy

Increased expression of tetherin at the host cell surface can suppress the release and replication of wild-type HIV-1 strains in cell culture (Neil et al., 2007; Sauter et al., 2009). IFN-α treatment and hence the induction of tetherin and other host restriction factors is known to reduce HIV-1 viremia in infected patients; however, these effects are often transient and accompanied by adverse reactions, such as flu-like symptoms and depression. A major problem is that IFN-α has both beneficial effects, because it inhibits virus replication, and harmful consequences, as it contributes to immune activation that helps to drive progression to AIDS (Herbeuval and Shearer, 2007). Notably, differences in the induction of the type I IFN immune response may distinguish pathogenic and nonpathogenic primate lentiviral infections. During the acute phase of infection, a strong type I IFN response is activated by both pathogenic and nonpathogenic lentiviruses, but this response is rapidly controlled and returns to basal levels only in nonpathogenic virus infections (Bosinger et al., 2009; Jacquelin et al., 2009). Thus, effective downmodulation of the type I IFN response may help the natural nonhuman primate hosts of SIVs to prevent the harmful chronic immune activation that drives progression to AIDS in HIV-1-infected individuals.

Another study on gender differences in HIV-1 infection suggests that the favorable and adverse effects of IFN-α may compensate each other. Plasmacytoid dendritic cells derived from women produce more IFN-α in response to HIV-1 infection, and women tend to have lower viral loads than men (Meier et al., 2009). On average, women progress to AIDS about as fast as men do. At the same viral loads, however, women show higher levels of immune activation and faster disease progression. Thus, it is questionable whether long-term clinical benefits can be achieved with IFN-α treatment. It may be possible to induce tetherin expression in a more specific manner (i.e., without causing systemic inflammation) or only at specific sites. Another strategy is to develop specific inhibitors of the viral antagonists of tetherin. But even complete loss of Vpu does not entirely impair the ability of HIV-1 to replicate in peripheral blood mononuclear cell cultures or in ex vivo-infected human lymphoid tissues (Neil et al., 2007; Schindler et al., 2010), suggesting that this strategy may not be very efficient. Nonetheless, further studies that induce tetherin expression or block its viral antagonists are required, particularly as tetherin targets the plasma membrane of the host cell that becomes the viral envelope. Tetherin is effective against a large number of viral pathogens, and it will be difficult for HIV-1 and other viruses to develop resistance to this host restriction factor.

Perspectives

We are only beginning to understand the complex interactions between viral pathogens and their hosts. For example, additional host restriction factors remain to be discovered, and the functions of many genes induced by IFN-α are only starting to be elucidated. One caveat is that most of the data about tetherin and the viral proteins that antagonize

it has been obtained using transfected cells that are not usually susceptible to HIV or SIV infection. To elucidate the role of tetherin and its antagonists in viral release, replication, pathogenesis, and transmission, it will be important to study replication-competent viruses in primary cells, ex vivo explant tissues, and animal models. Such studies should also reveal whether Vpu is a more effective tetherin antagonist than Nef, which may help to clarify why HIV-1 evolved to cause greater chronic immune activation than natural SIV infections (Kirchhoff, 2009). Furthermore, such analyses are needed to accurately assess whether the induction of host restriction factors or inhibition of their viral antagonists represent useful therapeutic strategies. The discovery of tetherin and other host restriction factors may also lead to the development of improved animal models. Finally, the recent generation of an artificial tetherin (Perez-Caballero et al., 2009) suggests that it may be possible to develop improved restriction factors with broad-based antiviral activity that are resistant to the action of viral antagonists. Further research will not only provide exciting new insights into the struggle between viruses and their hosts but may also lead to new therapeutic interventions for treating HIV and other viral infections.

Supplemental Information

Supplemental Information includes one table and can be found with this article online at doi:10.1016/j.cell.2010.04.022.

ACKNOWLEDGMENTS

We thank Beatrice H. Hahn and Guido Silvestri for helpful comments. The authors are supported by Deutsche Forschungsgemeinschaft and the National Institutes of Health.

REFERENCES

Alexander, L., Du, Z., Howe, A.Y., Czajak, S., and Desrosiers, R.C. (1999). J. Virol. *73*, 5814–5825.

Bailes, E., Gao, F., Bibollet-Ruche, F., Courgnaud, V., Peeters, M., Marx, P.A., Hahn, B.H., and Sharp, P.M. (2003). Science *300*, 1713.

Bartee, E., McCormack, A., and Früh, K. (2006). PLoS Pathog. *2*, e107.

Beignon, A.S., McKenna, K., Skoberne, M., Manches, O., DaSilva, I., Kavanagh, D.G., Larsson, M., Gorelick, R.J., Lifson, J.D., and Bhardwaj, N. (2005). J. Clin. Invest. *115*, 3265–3275.

Blasius, A.L., Giurisato, E., Cella, M., Schreiber, R.D., Shaw, A.S., and Colonna, M. (2006). J. Immunol. *177*, 3260–3265.

Bosinger, S.E., Li, Q., Gordon, S.N., Klatt, N.R., Duan, L., Xu, L., Francella, N., Sidahmed, A., Smith, A.J., Cramer, E.M., et al. (2009). J. Clin. Invest. *119*, 3556–3572.

Cao, W., Bover, L., Cho, M., Wen, X., Hanabuchi, S., Bao, M., Rosen, D.B., Wang, Y.H., Shaw, J.L., Du, Q., et al. (2009). J. Exp. Med. *206*, 1603–1614.

Douglas, J.L., Viswanathan, K., McCarroll, M.N., Gustin, J.K., Früh, K., and Moses, A.V. (2009). J. Virol. *83*, 7931–7947.

Dubé, M., Roy, B.B., Guiot-Guillain, P., Binette, J., Mercier, J., Chiasson, A., and Cohen, E.A. (2010). PLoS Pathog. *6*, e1000856.

Gao, F., Yue, L., White, A.T., Pappas, P.G., Barchue, J., Hanson, A.P., Greene, B.M., Sharp, P.M., Shaw, G.M., and Hahn, B.H. (1992). Nature *358*, 495–499.

Goffinet, C., Allespach, I., Homann, S., Tervo, H.M., Habermann, A., Rupp, D., Oberbremer, L., Kern, C., Tibroni, N., Welsch, S., et al. (2009). Cell Host Microbe *5*, 285–297.

Göttlinger, H.G., Dorfman, T., Cohen, E.A., and Haseltine, W.A. (1993). Proc. Natl. Acad. Sci. USA *90*, 7381–7385.

Gummuluru, S., Kinsey, C.M., and Emerman, M. (2000). J. Virol. *74*, 10882–10891.

Gupta, R.K., Hué, S., Schaller, T., Verschoor, E., Pillay, D., and Towers, G.J. (2009). PLoS Pathog. *5*, 1000443.

Haupt, S., Donhauser, N., Chaipan, C., Schuster, P., Puffer, B., Daniels, R.S., Greenough, T.C., Kirchhoff, F., and Schmidt, B. (2008). J. Virol. *82*, 8900–8905.

Herbeuval, J.P., and Shearer, G.M. (2007). Clin. Immunol. *123*, 121–128.

Hinz, A., Miguet, N., Natrajan, G., Usami, Y., Yamanaka, H., Renesto, P., Hartlieb, B., McCarthy, A.A., Simorre, J.-P., Gottlinger, H., and Weissenborn, W. (2010). Cell Host Microbe. Published online April 15, 2010. 10.1016/j.chom2010,03.005.

Jacquelin, B., Mayau, V., Targat, B., Liovat, A.S., Kunkel, D., Petitjean, G., Dillies, M.A., Roques, P., Butor, C., Silvestri, G., et al. (2009). J. Clin. Invest. *119*, 3544–3555.

Jia, B., Serra-Moreno, R., Neidermyer, W., Rahmberg, A., Mackey, J., Fofana, I.B., Johnson, W.E., Westmoreland, S., and Evans, D.T. (2009). PLoS Pathog. *5*, 1000429.

Jouvenet, N., Neil, S.J., Zhadina, M., Zang, T., Kratovac, Z., Lee, Y., McNatt, M., Hatziioannou, T., and Bieniasz, P.D. (2009). J. Virol. *83*, 1837–1844.

Kaletsky, R.L., Francica, J.R., Agrawal-Gamse, C., and Bates, P. (2009). Proc. Natl. Acad. Sci. USA *106*, 2886–2891.

Kirchhoff, F. (2009). Nat. Rev. Microbiol. *7*, 467–476.

Kirchhoff, F., Münch, J., Carl, S., Stolte, N., Mätz-Rensing, K., Fuchs, D., Haaft, P.T., Heeney, J.L., Swigut, T., Skowronski, J., and Stahl-Hennig, C. (1999). J. Virol. *73*, 8371–8383.

Kupzig, S., Korolchuk, V., Rollason, R., Sugden, A., Wilde, A., and Banting, G. (2003). Traffic *4*, 694–709.

Le Tortorec, A., and Neil, S.J. (2009). J. Virol. *83*, 11966–11978.

Malim, M.H., and Emerman, M. (2008). Cell Host Microbe *3*, 388–398.

Mandl, J.N., Barry, A.P., Vanderford, T.H., Kozyr, N., Chavan, R., Klucking, S., Barrat, F.J., Coffman, R.L., Staprans, S.I., and Feinberg, M.B. (2008). Nat. Med. *14*, 1077–1087.

Mangeat, B., Gers-Huber, G., Lehmann, M., Zufferey, M., Luban, J., and Piguet, V. (2009). PLoS Pathog. *5*, e1000574.

Mansouri, M., Viswanathan, K., Douglas, J.L., Hines, J., Gustin, J., Moses, A.V., and Früh, K. (2009). J. Virol. *83*, 9672–9681.

Mauclère, P., Loussert-Ajaka, I., Damond, F., Fagot, P., Souquières, S., Monny Lobe, M., Mbopi Keou, F.X., Barré-Sinoussi, F., Saragosti, S., Brun-Vézinet, F., et al. (1997). AIDS *15*, 445–453.

McNatt, M.W., Zang, T., Hatziioannou, T., Bartlett, M., Fofana, I.B., Johnson, W.E., Neil, S.J., and Bieniasz, P.D. (2009). PLoS Pathog. *5*, e1000300.

Meier, A., Chang, J.J., Chan, E.S., Pollard, R.B., Sidhu, H.K., Kulkarni, S., Wen, T.F., Lindsay, R.J., Orellana, L., Mildvan, D., et al. (2009). Nat. Med. *15*, 955–959.

Mitchell, R.S., Katsura, C., Skasko, M.A., Fitzpatrick, K., Lau, D., Ruiz, A., Stephens, E.B., Margottin-Goguet, F., Benarous, R., and Guatelli, J.C. (2009). PLoS Pathog. *5*, 1000450.

Miyagi, E., Andrew, A.J., Kao, S., and Strebel, K. (2009). Proc. Natl. Acad. Sci. USA *106*, 2868–2873.

Miyakawa, K., Ryo, A., Murakami, T., Ohba, K., Yamaoka, S., Fukuda, M., Guatelli, J., and Yamamoto, N. (2009). PLoS Pathog. *5*, 1000700.

Moore, R.C., Lee, I.Y., Silverman, G.L., Harrison, P.M., Strome, R., Heinrich, C., Karunaratne, A., Pasternak, S.H., Chishti, M.A., Liang, Y., et al. (1999). J. Mol. Biol. *292*, 797–817.

Neil, S., and Bieniasz, P. (2009). J. Interferon Cytokine Res. *29*, 569–580.

Neil, S.J., Eastman, S.W., Jouvenet, N., and Bieniasz, P.D. (2006). PLoS Pathog. *2*, e39.

Neil, S.J., Sandrin, V., Sundquist, W.I., and Bieniasz, P.D. (2007). Cell Host Microbe *2*, 193–203.

Neil, S.J., Zang, T., and Bieniasz, P.D. (2008). Nature *451*, 425–430.

Pais-Correia, A.M., Sachse, M., Guadagnini, S., Robbiati, V., Lasserre, R., Gessain, A., Gout, O., Alcover, A., and Thoulouze, M.I. (2010). Nat. Med. *16*, 83–89.

Perez-Caballero, D., Zang, T., Ebrahimi, A., McNatt, M.W., Gregory, D.A., Johnson, M.C., and Bieniasz, P.D. (2009). Cell *139*, 499–511.

Plantier, J.C., Leoz, M., Dickerson, J.E., De Oliveira, F., Cordonnier, F., Lemée, V., Damond, F., Robertson, D.L., and Simon, F. (2009). Nat. Med. *15*, 871–872.

Rollason, R., Korolchuk, V., Hamilton, C., Schu, P., and Banting, G. (2007). J. Cell Sci. *120*, 3850–3858.

Rollason, R., Korolchuk, V., Hamilton, C., Jepson, M., and Banting, G. (2009). J. Cell Biol. *184*, 721–736.

Sakuma, T., Noda, T., Urata, S., Kawaoka, Y., and Yasuda, J. (2009). J. Virol. *83*, 2382–2385.

Sauter, D., Schindler, M., Specht, A., Landford, W.N., Münch, J., Kim, K.-A., Votteler, J., Schubert, U., Bibollet-Ruche, F., Keele, B.F., et al. (2009). Cell Host Microbe *6*, 409–421.

Schindler, M., Münch, J., Kutsch, O., Li, H., Santiago, M.L., Bibollet-Ruche, F., Müller-Trutwin, M.C., Novembre, F.J., Peeters, M., Courgnaud, V., et al. (2006). Cell *125*, 1055–1067.

Schindler, M., Rajan, D., Banning, C., Wimmer, P., Koppensteiner, H., Iwanski, A., Specht, A., Sauter, D., Dobner, T., and Kirchhoff, F. (2010). Retrovirology *7*, 1.

Schubert, U., and Strebel, K. (1994). J. Virol. *68*, 2260–2271.

Strebel, K., Klimkait, T., Maldarelli, F., and Martin, M.A. (1989). J. Virol. *63*, 3784–3791.

Van Damme, N., Goff, D., Katsura, C., Jorgenson, R.L., Mitchell, R., Johnson, M.C., Stephens, E.B., and Guatelli, J. (2008). Cell Host Microbe *3*, 245–252.

Van Heuverswyn, F., and Peeters, M. (2007). Curr. Infect. Dis. Rep. *9*, 338–346.

Varthakavi, V., Smith, R.M., Bour, S.P., Strebel, K., and Spearman, P. (2003). Proc. Natl. Acad. Sci. USA *100*, 15154–15159.

Vendrame, D., Sourisseau, M., Perrin, V., Schwartz, O., and Mammano, F. (2009). J. Virol. *83*, 10527–10537.

Zhang, F., Wilson, S.J., Landford, W.C., Virgen, B., Gregory, D., Johnson, M.C., Munch, J., Kirchhoff, F., Bieniasz, P.D., and Hatziioannou, T. (2009). Cell Host Microbe *6*, 54–67.